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| 08/989,896 | 12/12/1997 | MATHIAS GEHRMANN | 05552.1337-0 | 9415 |

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EXAMINER

SAUNDERS, DAVID A

ART UNIT PAPER NUMBER

1644

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
984,896

Applicant(s)
GEHRMANN et al

Examiner
SAUNDERS

Group Art Unit
1647

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 7/22/03
- ☒ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1-22, 25-34 is/are pending in the application.
- Of the above claim(s) 14-22 is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-9, 25-28, 30, 33-34 is/are rejected.
- ☒ Claim(s) 10-13, 29, 31-32 is/are objected to.
- ☒ Claim(s) 1-22, 25-34 are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____.
 - ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Other _____

Office Action Summary

The amendment of 7/22/03 has been entered.

Claims 1-22 and 25-34 are pending with claims 1-13 and 25-34 under examination.

Examiner notes that, in action of 4/29/03, at page 14, line 1 "compels" should have read as --copies--.

Applicant's amendment, urgings and exhibit have overcome all 112, first and second paragraph rejections of record.

Due to applicant's urgings the 102 rejection of claim 34 over Bagshawe (WO 93/13805 has been withdrawn).

Claim 34 is rejected under 35 U.S.C. 102(e) as being anticipated by Hellstrom et al. (5,869,045).

As previously noted (page 19). Hellstrom et al. show a fusion polypeptide with an sFv binding portion linked by the synthetic linker (GlyGlyGlyGlySer)₃ to a prodrug activating enzyme portion. Applicant has urged that the examiner has misinterpreted the reference as to how the linker was formed by a PCR method. Whether the examiner was correct or in error is not relevant to the claimed invention, which is to the fusion polypeptide resulting from the linking and not to a method of forming such. Whether one uses the method recited in part B) of claim 34 or the method of Hellstrom et al. makes no difference; a resulting fusion polypeptide having precisely the same exemplified linker is formed by either method.

Claim 34 is rejected under 35 U.S.C. 102(e) as being entirely anticipated by Borstel et al. (6,258,360).

The rejection is maintained for the same reasons set forth supra with respect to Hellstrom et al.

Claims 1-9, 25-27, 30 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al. (Brit. J. Cancer 65,235,1992) or Seeman et al. (EP 0,050,215/CA 2,062,047) or Eaton et al. (EP 0,392,745) in view of Huston et al. (5,258,498 or WO 88/09344) and Bosslet et al. (5,591,828 or EP 0,040,097).

Applicant has traversed (pages 20-21) the rejection by arguing that Huston et al. merely suggest that multiple sFv regions may be fused to an enzyme, without having exemplified such; and applicant has argued that there is no reason to have expected success in making such a fusion construct. These arguments are unconvincing because it is not required that a reference show every embodiment by way of example. Also applicant has offered no factual reasons as to why there would have not been a reasonable expectation of success in producing a multiple sFv – enzyme fusion protein with functional activities in both portions of the protein. Examiner also notes that none of applicant's examples show production of a fusion polypeptide having multiple sFv domains fused to an enzyme. If Huston et al would not have led one to an expectation of success in providing a fusion protein with multiple, active sFv domains, then neither has applicant. Cited combination of art is as enabling as applicant's own disclosure.

Applicant has also urged (page 19) that the examiner has merely argued that Fab, Fv and sFv are functionally equivalent without showing that they are structurally equivalent. To the contrary, the examiner notes that Huston et al. designed their sFv to have the three dimensional structure of the corresponding Fab and Fv fragments. See col. 13, line 23 + ; col. 22, lines 25+.

Applicant also urges (page 21) that Huston et al. produce their fusion proteins in bacteria, while Bosslet et al. do so with BHK cells. Examiner notes that Huston et al. in fact, also teach production in eukaryotic hosts (col. 20, lines 5-7). Thus one would have no reason to not expect the baby hamster kidney (BHK) cells of Bosslet et al. to be appropriate for production of fusion proteins containing sFv.

Applicant has also argued (page 21) that the examiner has not provided evidence that one would have been able to provide bivalent or multivalent sFv constructs, without significantly increasing the size of the fusion protein. Applicant argues examiner is relying upon "general knowledge". In fact, examiner is relying upon what Huston et al. teach with respect to such general knowledge. From col. 1, lines 32 + they teach an L-chain has a M.W. of 25,000 and an H-chain of 50,000. Thus the Fab of Eaton et al. Bosslet et al. and Seeman et al. primary references would contribute 50,000 to the M.W. of there taught fusion proteins.

To estimate the M.W. of an sFv, the examiner refers to the teachings of Huston et al. at col. 27 with respect to the FB-sFv fusion protein. This has a M.W. of 34,000 (col. 27, line 39). Of this ca. 5,000 is contributed by the 43 amino acids of the FB. -i.e. 43×110 (average amino acid residue M.W.) This leaves $34,000 - 5,000$ or ca. 29,000 as the M.W. of an sFv. Two sFv segments would

thus contribute a M.W. of 58,000 to a fusion protein; this is barely more than the 50,000 of the Fab in the fusion constructs of the primary references. As to motivation to keep the M.W. as low as possible, see Huston et al. at col. 8, lines 56-63 and col. 13, lines 2-7.

Finally applicant has argued that Huston et al. do not teach the linking by PCR, as recited in part (b) of claims 1 and 34. Examiner has noted supra (102 rejection over Hellstrom et al.) that this argument is not relevant to claims to a polypeptide having the linkers is the same polypeptide, no matter how it was produced. ^{Since any polypeptide}

Due to applicant's urgings the examiner has withdrawn the following 103 rejections, employing that stated above in view of various tertiary references:

- 1) The rejection of claims 1, 11-12 and 31-32 employing Ong et al. and Bagshawe et al. as tertiary references.
- 2) The rejection of claims 1, 10, 13 and 29 employing Ong et al. and Bagshawe et al., as tertiary references, and Goochee et al., as a quaternary references.

Examiner concurs that Huston et al. does not discuss the impact of glycosylation upon the sFv constructs. Due to their much smaller size, as compared to antibodies, it is not predictable as to whether or not these would retain binding activity upon glycosylation.

The following rejection based upon the tertiary reference of Bagshawe et al. (WO 88/07378) is maintained:

Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al., Seeman et al. or Eaton et al. in view of Huston et al. and Bosslet et al. as applied to claims 1-9, 25, 27, 30 and 33 above, and further in view of Bagshawe et al. (WO 88/07378).

Applicant has traversed by arguing that the providing the linker by the P²CR reaction recited in claims 1 and 34 is not taught by Bagshawe et al. as examiner has noted supra, this argument is irrelevant to claims to a protein product.

The following rejections based upon Winter et al. as a primary reference are maintained:

Claims 1-4, 8-9, 25-26 and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. (6,248,516) in view of Huston et al. (5,258,498 or WO 88/09344) for reasons of record.

Claims 1-2, 4-5, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Huston et al. as applied to claims 1-4, 8-9, 25-26 and 33-34 above, and further in view of Seeman et al. for reasons of record.

Claims 1, 6, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Huston et al. as applied to claims 1-4, 8-9, 25-26 and 33-34 above, and further in view of Eaton et al., for reasons of record.

Claims 1, 6 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al., in view of Huston et al. as applied to claims 1-4, 8-9, 25-26 and 33-34 above, and further in view of Bagshawe et al. (WO 88/07378), for reasons of record.

All of these rejections have been traversed on the base that the references fail to teach the linking method recited in claims 1 and 34, part (b) of each. The examiner reiterates, that thus argument is unconvincing.

For reasons noted further supra, examiner has withdrawn the following rejections based on Winter et al. in view of various tertiary references;

- 1) The rejection of claims 1-2, 9, 11-12 and 31-32 further in view of Ong et al. and Bagshawe et al., as tertiary references.
- 2) The rejection of claims 1, 10, 13 and 29 further in view of Ong et al. and Bagshawe et al. as tertiary references, and Goochee et al., as a quaternary reference.

Applicants' urgings of 7/22/03 have been considered but are unconvincing, except as noted above.

Claims 10-13, 29 and 31-32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, Ph.D., whose telephone number is (703) 308-3976. The examiner can normally be reached on Monday-Thursday from 8:00 a.m. to 5:30 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306

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Any inquiry of a general nature or relating to the status of this application
or proceeding should be directed to the receptionist whose telephone number is
(703) 308-0196.

D. Saunders:jmr

November 21, 2003

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644